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[Chest Infections Original Research]

CHEST

Persistent Exertional Intolerance After COVID-19

Insights From Invasive Cardiopulmonary Exercise Testing

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BACKGROUND: Some patients with COVID-19 who have recovered from the acute infection after experiencing only mild symptoms continue to exhibit persistent exertional limitation that often is unexplained by conventional investigative studies.

RESEARCH QUESTION: What is the pathophysiologic mechanism of exercise intolerance that underlies the post-COVID-19 long-haul syndrome after COVID-19 in patients without cardiopulmonary disease?

STUDY DESIGN AND METHODS: This study examined the systemic and pulmonary hemodynamics, ventilation, and gas exchange in 10 patients who recovered from COVID-19 and were without cardiopulmonary disease during invasive cardiopulmonary exercise testing (iCPET) and compared the results with those from 10 age- and sex-matched control participants. These data then were used to define potential reasons for exertional limitation in the cohort of patients who had recovered from COVID-19.

RESULTS: The patients who had recovered from COVID-19 exhibited markedly reduced peak exercise aerobic capacity (oxygen consumption [VO_2]) compared with control participants (70 ± 11% predicted vs 131 ± 45% predicted; $P < .0001$). This reduction in peak VO_2 was associated with impaired systemic oxygen extraction (ie, narrow arterial-mixed venous oxygen content difference to arterial oxygen content ratio) compared with control participants (0.49 ± 0.1 vs 0.78 ± 0.1; $P < .0001$), despite a preserved peak cardiac index (7.8 ± 3.1 L/min vs 8.4±2.3 L/min; $P > .05$). Additionally, patients who had recovered from COVID-19 demonstrated greater ventilatory inefficiency (ie, abnormal ventilatory efficiency [VE/VCO_2] slope: 35 ± 5 vs 27 ± 5; $P = .01$) compared with control participants without an increase in dead space ventilation.

INTERPRETATION: Patients who have recovered from COVID-19 without cardiopulmonary disease demonstrate a marked reduction in peak VO_2 from a peripheral rather than a central cardiac limit, along with an exaggerated hyperventilatory response during exercise.

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KEY WORDS: cardiopulmonary exercise test; COVID-19; hemodynamics; iCPET; long haulers; post-COVID-19 syndrome

ABBREVIATIONS: CaO_2 = arterial oxygen content; CO = cardiac output; CPET = cardiopulmonary exercise testing; DO_2 = oxygen delivery; EO_2 = systemic oxygen extraction; iCPET = invasive cardiopulmonary exercise testing; SV = stroke volume; SVI = stroke volume index; VE/VCO_2 = ventilatory efficiency; VO_2 = oxygen consumption

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Take-home Points

Study Question: What is the pathophysiologic mechanism of exercise intolerance that underlies post-COVID-19 long-haul syndrome in patients with COVID-19 without cardiopulmonary disease?

Results: Patients who have recovered from COVID-19 demonstrate reduced peak exercise aerobic capacity with impaired systemic oxygen extraction and abnormal ventilatory efficiency slope.

Interpretation: Patients without cardiopulmonary disease who have recovered from COVID-19 demonstrate a marked reduction in peak oxygen consumption from a peripheral rather than a central cardiac limit, along with an exaggerated hyperventilatory response during exercise.

Globally, more than 100 million confirmed cases of COVID-19 caused by SARS-CoV-2 infection have been reported. The acute manifestations of SARS-CoV-2 infection can involve the pulmonary, cardiovascular, neurologic, hematologic, and GI systems.[1] Persistent physical symptoms after acute COVID-19 are common and includes fatigue, dyspnea, chest pain, cough, and neurocognitive symptoms.[2-6] In one retrospective study of approximately 1,300 hospitalized patients with COVID-19 discharged to home, only 40% of patients were independent in all activities of daily living at 30 days,[6] and almost 40% of patients were unable to return to normal activities at 60 days after hospital discharge.[7] Several recent studies have reported persistent symptoms among patients who demonstrated mild COVID-19 months after recovery from the acute illness.[8-10] Persistent cardiorespiratory symptoms in those who have survived COVID-19 can be categorized into two clinical entities: (1) those directly related to organ injury or iatrogenic consequences during the acute phase and (2) those with persistent symptoms, including a decrease in exercise capacity determined objectively by cardiopulmonary exercise testing (CPET), with normal findings from pulmonary function testing, resting echocardiography, and CT scan of the chest months after the onset of acute symptoms,[11,12] the so-called post-COVID-19 long-haul syndrome.

In a recent study, Baratto and colleagues[13] showed that during CPET performed at the time of hospital discharge, patients who have recovered from COVID-19 exhibited a hyperventilatory response and reduced exercise capacity. The latter was attributed primarily to underlying anemia resulting in both reduced systemic oxygen delivery and extraction. However, the pathophysiologic basis for the persistent exertional and functional limitation among patients who have had COVID-19 and who have long since recovered from mild acute illness remains unknown. Accordingly, in the current study, we aimed to help characterize further persistent exercise intolerance among patients who have recovered from COVID-19 without evidence of cardiopulmonary disease or anemia using invasive CPET (iCPET).

Methods

Study Population and Design

We consecutively enrolled all patients who had recovered from COVID-19 and were referred to the Brigham and Women's Hospital Dyspnea Clinic (Boston, MA) and the Yale New Haven Hospital Pulmonary Vascular Disease Clinic (New Haven, CT) between February and June 2021 for unexplained exercise intolerance. The study protocol was approved by Partners Healthcare Human Research Committee (Identifier: 2011P000272) and Yale University Institutional Review Board (Identifier: IRB 2000024783). All patients signed informed consent and agreed to have their anonymized clinical and investigative data used for research purposes.

All patients underwent conventional investigative testing during outpatient clinic evaluation, including CT scan of the chest, pulmonary function test, and resting echocardiography. In none of the patients were test results deemed contributory to the persistent exertional limitation before iCPET referral. Specifically, no evidence was found of parenchymal lung disease on chest CT imaging, and all patients demonstrated left ventricle ejection fraction of > 50% with no evidence of moderate or severe valvular heart disease, no evidence of right-to-left intracardiac shunt defect on resting right heart catheterization and echocardiography, and no evidence of acute coronary syndrome defined by ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, unstable angina, or a combination thereof during exercise testing.

Invasive Cardiopulmonary Exercise Testing

Our method for invasive CPET was described previously.[14-18] Right heart catheterization was performed in the supine position with a

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five-port pacing pulmonary artery catheter (Edwards LifeSciences) inserted percutaneously under fluoroscopic and ultrasound guidance into the internal jugular vein and a radial artery catheter concurrently placed in the radial artery. Patients underwent a symptom-limited incremental CPET using an upright cycle ergometer with a breath-by-breath assessment of gas exchange (ULTIMA CPX; Medical Graphics Corporation) along with continuous 12-lead electrocardiography monitoring. Patients underwent 2 min of rest followed by 2 min of unloaded cycling at 40 to 60 RPM. Work rate then was increased continuously using a ramp protocol at 5, 10, 15, or 20 W/min depending on the patient's functional status, until peak exercise was achieved as evident either by peak respiratory exchange ratio of $>$ 1.10 or peak heart rate of $>$ 85% predicted. Pulmonary and systemic hemodynamics were monitored continuously and simultaneously during exercise (Xper Cardio Physiomonitoring System; Phillips). Pulmonary pressures were recorded at the end of passive exhalation. When respirophasic changes persisted, an electronic average over three respiratory cycles was used.[19] Arterial and mixed venous blood gases and pH were collected during each minute of exercise, and the arterial-mixed venous oxygen content difference was calculated. Systemic oxygen extraction (EO_2) was calculated as arterial oxygen content (CaO_2) minus CvO_2 divided by CaO_2. Fick cardiac output and stroke volume were determined every minute. Oxygen delivery (DO_2) was calculated by multiplying cardiac output by the CaO_2. Physiologic dead space was calculated as: $VD/VT = (Pa_{CO_2} - PETCO_2) / Pa_{CO_2}$, where VD is dead space volume, VT is tidal volume, Pa_{CO_2} is the P_{CO_2} in arterial blood, and $PETCO_2$ is the mixed expired P_{CO_2}.

Pulmonary vascular resistance was calculated as: mean pulmonary artery pressure minus pulmonary artery wedge pressure divided by cardiac output, expressed in Woods units. Stroke volume (SV) was calculated as cardiac output (CO) divided by the heart rate. CO and SV were indexed to body surface area to obtain both cardiac index and SV index. Pulmonary artery compliance was calculated as the ratio of SV to pulmonary artery pulse pressure and was expressed as milliliters per millimeter of mercury. Total pulmonary resistance was calculated as mean pulmonary artery pressure divided by CO as expressed in Woods units.

To investigative further the determinants of exercise limitation in patients who have recovered from COVID-19, we identified 10 age- and sex-matched control participants from our iCPET database. This cohort consisted of symptomatic patients who previously underwent iCPET for clinical investigation of exertional intolerance, but who exhibited a normal physiological limit to exercise defined by a peak oxygen uptake (peak oxygen consumption [VO_2]) and peak CO of $\geq$ 80% predicted.

Statistical Analysis

Unless otherwise stated, values are presented as mean $\pm$ SD. Comparisons of baseline characteristics, resting hemodynamics, and CPET parameters between patients who have recovered from COVID-19 and control participants were performed using an independent *t* test for normally distributed data and the Wilcoxon rank-sum test for data nonnormally distributed data. The χ^2 test was used to analyze dichotomous variables. A *P* value of $<$ .05 was considered significant. Statistical analyses were performed using GraphPad Prism version 9 software (GraphPad Software) and SAS version 9.4 software (SAS Institute, Inc.).

Results

Demographic and Clinical Characteristics

We included 10 patients who have recovered from COVID-19 who at the time of iCPET were demonstrated negative results by polymerase chain reaction for SARS-CoV-2. Nine patients previously had experienced mild, acute SARS-CoV-2 infection that did not require hospitalization,[20] whereas one patient underwent a brief 2-day in-patient stay during which Remdesivir and corticosteroids were administered. Two patients were excluded during the enrollment period: one patient with long-standing history of fibrotic interstitial lung disease and another who exhibited iatrogenic chronotropic incompetence from B-adrenergic blocker therapy. The latter patient did not attain maximum exercise effort by either by peak respiratory exchange ratio of $>$ 1.10 or peak heart rate of $>$ 85% predicted.

No differences were found in age, hemoglobin concentration, BMI, medication use, or comorbidities between patients who had recovered from COVID-19 and control participants. Importantly, the average interval between onset of acute COVID-19 illness (ie, from the time of positive SARS-CoV-2 polymerase chain reaction results) to iCPET was 11 months (Table 1). Patients who had recovered from COVID-19 demonstrated normal resting right heart hemodynamic values. The baseline characteristics, comorbidities, resting right heart hemodynamics, and pulmonary function test results are summarized in Table 1.

Peak Exercise Hemodynamic Response

The maximum invasive CPET and cardiopulmonary hemodynamic data are summarized in Table 2. At peak exercise, patients who had recovered from COVID-19 exhibited markedly reduced aerobic capacity (ie, peak VO_2 $<$ 80% predicted) with a normal peak DO_2 and reduced EO_2 compared with control participants (Fig 1). Patients who had recovered from COVID-19 showed greater peak exercise mixed venous oxygen saturation (50 $\pm$ 10% vs 22 $\pm$ 5%; $P < .0001$) and peak VO_2 content (33 $\pm$ 6 mm Hg vs 27 $\pm$ 5 mm Hg; $P = .01$) compared with control participants. Additionally, patients who had recovered from COVID-19 exhibited a greater degree of ventilatory inefficiency compared with control participants (ie, abnormal ventilatory efficiency [VE/VCO_2] slope: 35 $\pm$ 5 vs 27 $\pm$ 5; $P = .01$) (Fig 2). Of the 10 patients who had recovered from COVID-19, only one patient demonstrated a VE/VCO_2 slope of

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TABLE 1] Baseline Characteristics and Resting Cardiopulmonary Hemodynamics

Variable	Patients Recovered from COVID-19 (n = 10)	Control Participants (n = 10)	*P* Value
Characteristics			
Age, y	48 ± 15	48 ± 8	.87
Female sex	9 (90)	8 (80)	.53
BMI, kg/m^2	28 ± 6	24 ± 6	.11
Hemoglobin, g/dL	13.4 ± 1.1	14.2 ± 1.4	.16
Interval from acute COVID-19 infection to iCPET, mo	11 ± 1	Not applicable	…
Comorbidities			
Systemic hypertension	2 (20)	3 (30)	.61
Diabetes	0	1 (10)	.30
Medications			
β-Adrenergic receptor blocker	1 (5)	1 (5)	1.00
ACE inhibitor or ARB	2 (20)	0	.13
Diuretics	0	1 (10)	.30
Pulmonary function test			
FEV_1, %	97 ± 1	100 ± 1	.34
FVC, %	96 ± 1	104 ± 1	.19
FEV_1 to FVC ratio, %	101 ± 3	98 ± 5	.18
Resting upright right heart catheterization			
SaO_2, %	98 (97-98)	98 (97-98)	.64
MvO_2, %	73 ± 3	66 ± 6	.01
Right atrial pressure, mm Hg	0 (0-1)	3 (0-4)	.35
Stroke volume index, mL/m^2	36.3 ± 10.3	40.3 ± 12.8	.44
Cardiac index, L/min/m^2	3.2 ± 0.6	2.8 ± 0.5	.13
mPAP, mm Hg	8 ± 1	12 ± 3	.002
PAWP, mm Hg	2 ± 2	5 ± 3	.01
PVR, WU	1.13 (0.87-1.52)	1.26 (0.95-2.01)	.44
PA compliance, mL/mm Hg	5.6 ± 2.4	7.7 ± 3.3	.13
SVR index, dynes/s/cm^5/m^2	2,554 ± 880	2,924 ± 487	.26

Data presented as No. (%),mean ± SD, or median (interquartile range). ACE = angiotensin converting enzyme; iCPET = invasive cardiopulmonary test; mPAP = mean pulmonary artery pressure; MvO_2 = mixed venous oxygen saturation; PA = pulmonary artery; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; SaO_2 = oxygen saturation in arterial blood; SVR = systemic vascular resistance; WU = Woods unit.

< 30 at 28.[21] In the patients who had recovered from COVID-19, a trend toward lower peak right atrial pressure (3 ± 4 mm Hg vs 6 ± 3 mm Hg; $P = .08$) was found, along with a significantly reduced left-side filling pressure (pulmonary artery wedge pressure, 8 ± 4 mm Hg vs 13 ± 3 mm Hg; $P = .01$). An appropriate decrease in dead space ventilation was found in patients who had recovered from COVID-19 from rest to peak exercise (0.39 ± 0.1 vs 0.22 ± 0.1; $P = .001$) (Fig 3). The total pulmonary resistance at peak exercise was normal in both groups (ie, peak total pulmonary resistance < 3 Woods units).

Discussion

In the current study, we demonstrate that nearly 1 year after recovery from mild disease, patients who experienced COVID-19 and had with decreased exercise tolerance, but no long-term cardiopulmonary disease sequelae, exhibited a peripheral, rather than a central, cardiac limit to aerobic exercise characterized by impaired systemic EO_2 with resulting increased peak exercise mixed venous oxygen saturation and peak VO_2 content. Additionally, they also demonstrated a hyperventilatory response during exercise from enhanced chemoreflex sensitivity.

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TABLE 2] Maximum Exercise Cardiopulmonary Hemodynamics

Variable	Patients Recovered from COVID-19 (n = 10)	Control Participants (n = 10)	*P* Value
Maximum CPET data			
Peak VO_2, % predicted	70 ± 11	131 ± 45	.001
Peak VO_2, mL/min/kg	16.7 ± 4.2	33.5 ± 12.9	.001
Peak heart rate, % predicted	84 ± 8	84 ± 2	.85
Delta $ETCO_2$, mm Hg	−0.5 (−4 to 1)	−1 (−2 to 13)	.57
Peak SaO_2, %	98 (98-98)	97 (97-98)	.01
Peak MvO_2, %	50 ± 10	22 ± 5	< .0001
Venous PO_2, mm Hg	33 ± 6	22 ± 2	.001
VE/VCO_2 slope	35 ± 5	27 ± 5	.01
CaO_2, mL/dL	18.6 ± 1.3	19.5 ± 2.3	.29
Peak DO_2, mL/kg/min	3.6 ± 1.4	4.2 ± 1.5	.33
Peak EO_2	0.49 ± 0.1	0.78 ± 0.1	< .0001
Peak exercise hemodynamics			
Cardiac output, % predicted	115 ± 44	123 ± 34	.64
Cardiac index, L/min/m^2	7.8 ± 3.1	8.4 ± 2.3	.59
Stroke volume index, mL/m^2	54.1 ± 20.8	63.5 ± 22.2	.34
RA pressure, mm Hg	3 ± 4	6 ± 3	.08
mPAP, mm Hg	18 ± 5	30 ± 4	< .0001
PAWP, mm Hg	8 ± 4	13 ± 3	.01
PVR, WU	0.69 ± 0.44	0.99 ± 0.36	.11
TPR, WU	1.2 ± 0.4	2.0 ± 0.4	.002
PA compliance, mL/mm Hg	4.7 ± 2.3	4.3 ± 2.1	.67
SVR index, dynes/s/cm^5/m^2	1,272 ± 398	1,119 ± 283	.33

Data are presented as No. (%), mean ± SD, or median (interquartile range). CaO_2 = arterial oxygen content; CPET = cardiopulmonary exercise testing; DO_2 = oxygen delivery; EO_2 = systemic oxygen extraction; $ETCO_2$ = end tidal CO_2; mPAP = mean pulmonary artery pressure; MvO_2 = mixed venous oxygen saturation; PA = pulmonary artery; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; SaO_2 = oxygen saturation in arterial blood; RA = right atrial; SVR = systemic vascular resistance; TPR = total pulmonary resistance; VE/VCO_2 = ventilatory efficiency; VO_2 = oxygen consumption; WU = Woods unit.

According to the Fick principle, in the absence of a pulmonary mechanical limitation, reduced peak VO_2 is the result of a blunted CO and cardiac index response, impaired systemic EO_2 (ie, arterial-mixed venous oxygen content difference), or both. In the current study, the depressed peak VO_2 in patients who had recovered from COVID-19 was driven primarily by reduced systemic EO_2 (Fig 1). In fact, the peak CO response was robust, representing on average 115% of the predicted value, and the DO_2 was preserved. We also demonstrated that in both control participants and patients who have recovered from COVID-19, throughout incremental exercise testing, increases in VO_2 were driven by increments in both EO_2 and cardiac index (Fig 1). However, unlike control participants, at 75% of peak VO_2 and at peak VO_2, further increases in VO_2 in patients who had recovered from COVID-19 were attenuated by limitations imposed by EO_2, rather than cardiac index.

The delivery and subsequent use of oxygen is determined by convective and diffusive processes. Convective oxygen delivery involves alveolar ventilation and the transport of hemoglobin-bound oxygen by the heart and systemic vasculature to the peripheral microcirculation (ie, DO_2). Diffusive oxygen delivery involves the diffusion of oxygen across the alveolar-pulmonary capillary membrane onto hemoglobin and the unloading of oxygen from hemoglobin in skeletal muscle capillaries where the process of aerobic mitochondrial respiration generates ATP. A study from Baratto and colleagues[13] demonstrated that the reduced systemic EO_2 among patients who have recovered from COVID-19 at time of hospital discharge was driven in part by reduced convective oxygen delivery from

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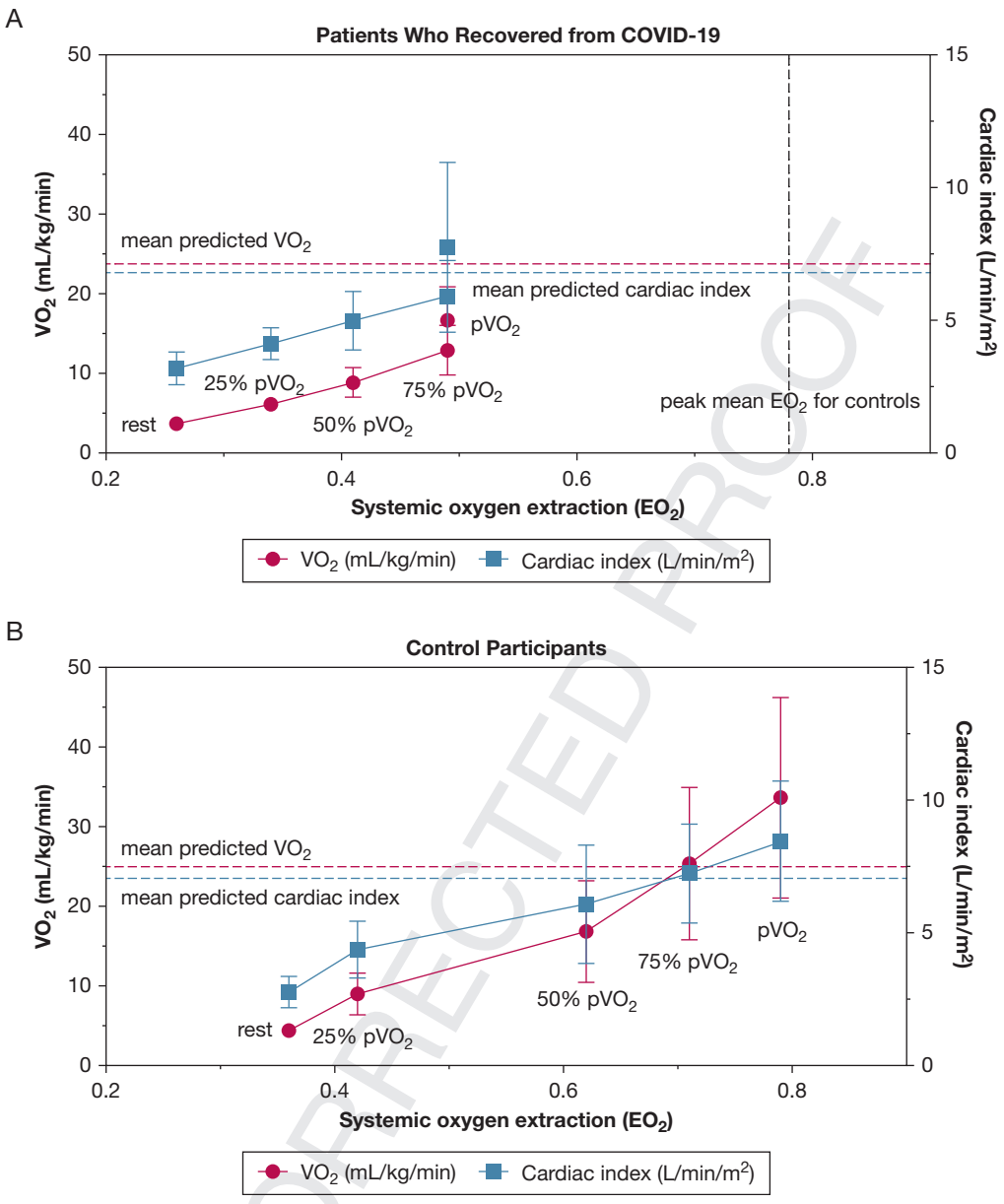

Figure 1 – *A-B, Graphs showing the components of the Fick principle in the patients who recovered from COVID-19 (A) and control participants (B) during maximum incremental invasive cardiopulmonary testing at rest, 25% of pVO_2, 50% of pVO_2, 75% of pVO_2, and at pVO_2. Data presented as mean ± SD. pVO_2 = peak oxygen consumption; VO_2 = oxygen consumption. EO_2 = systemic oxygen extraction.*

underlying anemia (ie, reduced CaO_2 and DO_2). Our findings differ from those of Baratto and colleagues for two main reasons. First, the current study examined patients who had recovered from COVID-19 with persistent exertional and functional limitation approximately 11 months after acute viral illness. Additionally, apart from one patient, these patients who had recovered from COVID-19 did not require in-patient care. Second, unlike the study from Baratto and colleagues, the current patients who recovered from COVID-19 did not have associated anemia or parenchymal lung disease. Importantly, we found that convective oxygen transport in the patients who recovered from COVID-19 was preserved (ie, normal DO_2). Therefore, the impaired EO_2 observed in the current study was attributed primarily to reduced oxygen diffusion in the peripheral microcirculation, resulting in increased peak exercise mixed venous oxygen saturation and peak VO_2 content (Table 2).

More recently, two noninvasive CPET studies in patients who have recovered from COVID-19 have been reported.[22,23] The first study by Rinaldo and colleagues[22]

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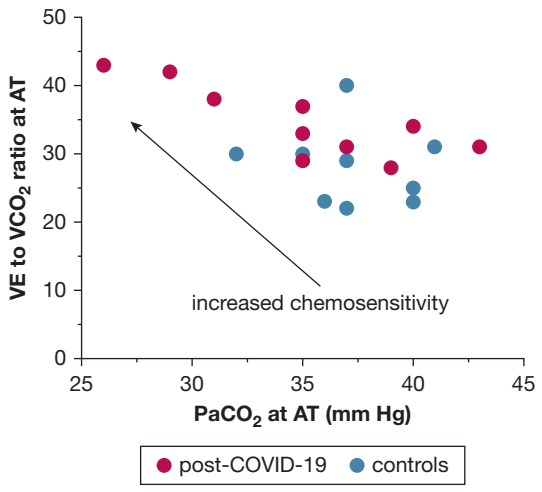

Figure 2 – *Graph showing abnormal ventilatory efficiency in patients who have recovered from COVID-19 at the AT. AT = anaerobic threshold; VE/VCO$_2$ = ventilatory efficiency.*

evaluated 75 patients 3 months after hospital discharge. Fifty-two percent and 24% of the patients who had recovered from COVID-19 were categorized as having critical and severe disease, respectively, whereas 63% of patients demonstrated residual parenchymal lung disease on chest CT imaging. The authors found that patients with reduced peak exercise capacity (defined by peak VO$_2$ of $<$ 85% predicted) attained anaerobic threshold early, but exhibited no pulmonary mechanical limit to exercise (ie, preserved breathing reserve index) with preserved ventilatory efficiency (ie, VE to VCO$_2$ ratio slope of 28 $\pm$ 3). Also, no correlation was found between reduction in peak exercise capacity with reduced diffusing capacity on lung function test or parenchymal lung disease on chest CT imaging. Based on these findings, the authors concluded that the reduced peak exercise capacity seen in the patients who had recovered from COVID-19 is because of deconditioning. The second study by Skjorten and colleagues[23] examined 189 patients also 3 months after hospital discharge, of whom 20% required ICU management.[23] The peak VO$_2$ (% predicted) was lower among patients who had recovered from COVID-19 and who required ICU management, but no difference was found in the breathing reserve and VE to VCO$_2$ ratio slope between patients treated in the ICU and those who were not. Across the entire cohort, reduced peak VO$_2$ ($<$ 80% predicted) was observed in 31% of participants. When compared with a reference population, patients who recovered from COVID-19 exhibited preserved ventilatory efficiency (ie, VE to VCO$_2$ ratio slope of 28 $\pm$ 5) and breathing reserve (30 $\pm$ 17%) along with preserved oxygen pulse (15 $\pm$ 4 mL/stroke). Accordingly, the authors concluded that deconditioning was the major cause of exercise limitation in the patients who had recovered from COVID-19. In our study of patients approximately 11 months after recovery from mild disease, deconditioning was an unlikely explanation for the impaired systemic EO$_2$. In fact, the findings of our study argue against muscle deconditioning as the cause of impaired EO$_2$. This is because the hallmark of deconditioning is reduced peak CO.[24] In the current study, among the patients who recovered from COVID-19, the peak CO (% predicted) was normal at 115 $\pm$ 44% predicted. Additionally, deconditioning causes little or no change in peak exercise EO$_2$.[24,25] Furthermore, the patients presented herein who had recovered from COVID-19 demonstrated lower low biventricular filling pressures, rather than the higher pressures encountered in detrained individuals, which is attributable to cardiac atrophy and reduced ventricular compliance.[26,27]

During exercise, the greater need for local tissue metabolism coupled with reduced availability of tissue oxygen results in greater production of local vasodilatory substances in the skeletal muscles. This mechanism, along with sympathetic nervous system-mediated vasoconstriction to nonexercising areas, allows for increased tissue oxygen delivery during exercise.[28] We recently demonstrated in a cohort of patients with chronic fatigue syndrome that systemic microcirculatory dysfunction with microvascular shunting (impaired systemic oxygen extraction) was prevalent particularly among patients who also exhibited small-fiber neuropathy on skin biopsy.[29] Immunohistochemical studies have shown that these small fibers regulate microvascular tone through sympathetic and parasympathetic cholinergic synapses of perivascular myocytes.[30] Although considerable overlap exists in the clinical presentation of patients with post-COVID-19 and chronic fatigue syndrome,[12] whether a similar neuropathologic mechanism is seen in the patients who have recovered from COVID-19 remains to be determined.

The other important finding of the current study is the exaggerated hyperventilatory response among the patients who recovered from COVID-19, as evident by the abnormal VE to VCO$_2$ ratio slope (Fig 2). Arterial CO$_2$ set point is influenced by acidemia, hypoxemia, baroreceptors in the pulmonary vasculature, and sympathetic nervous system hyperactivity.[31,32] VE to VCO$_2$ ratio is measured at the anaerobic threshold

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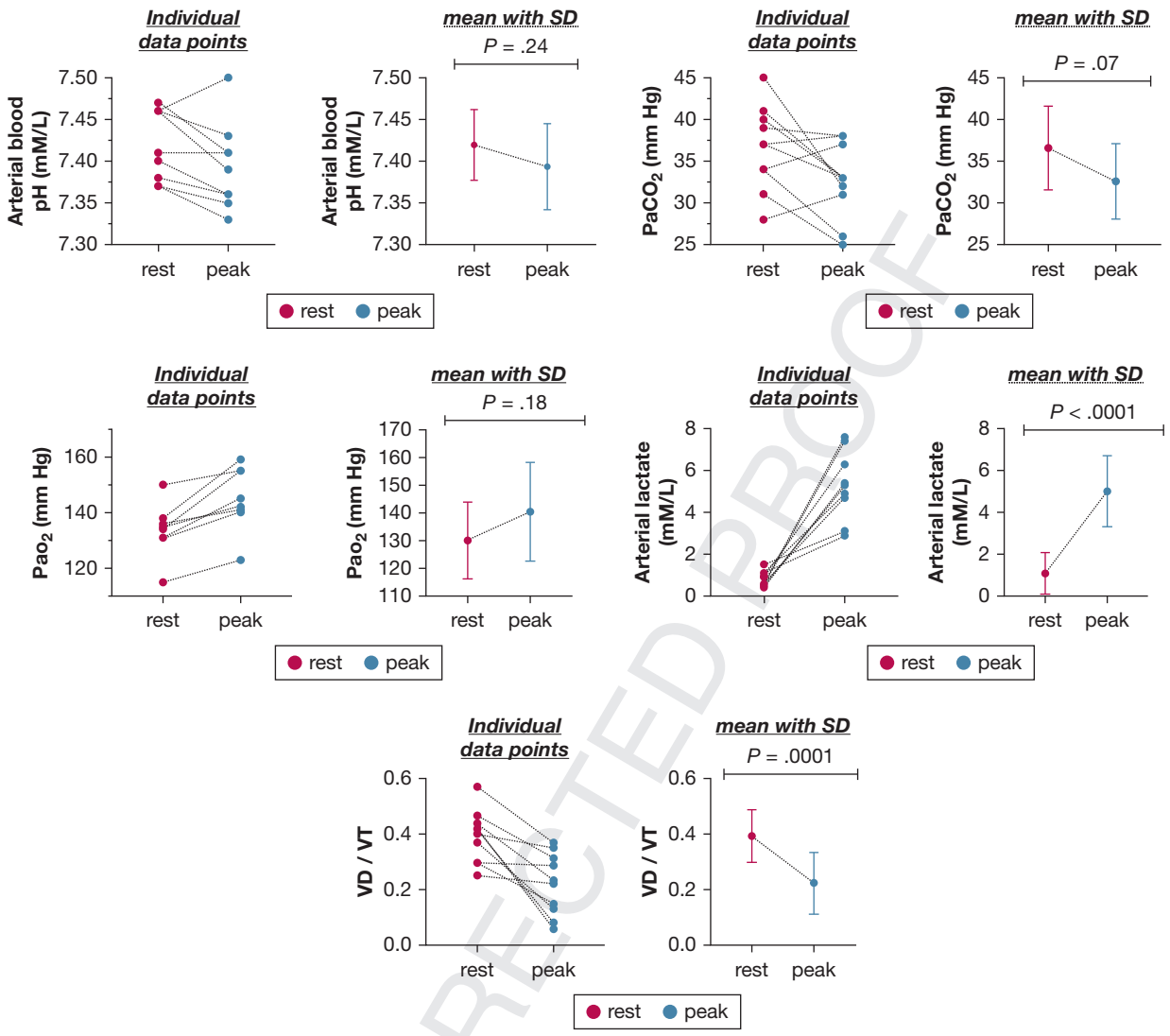

Figure 3 – *Graphs showing blood gas data from patients who have recovered from COVID-19 at rest and peak exercise. Data are presented as individual data point for each patient and mean ± SD, with blue dots representing data at rest and red dots representing data at peak exercise. P value obtained using independent t test. VD/VT = ratio of dead space to tidal volume.*

before the onset of anaerobic metabolism and lactic acidosis generation. Additionally, no evidence was found of resting or exercise pulmonary hypertension or interstitial lung disease with the expectant decrease in dead space ventilation seen during exercise (Figs 2, 3). The abnormal ventilatory efficiency in the patients who had recovered from COVID-19 thus can be attributed to enhanced peripheral mechanoergoreflex and metaboergoreflex sensitivity, rather than a primary cardiopulmonary or central mediated hyperventilation process.[33] In patients with heart failure, for example, skeletal muscle group III-IV afferents play an important role the exaggerated hyperventilatory response seen during exercise. These mechanoreceptors and metaboreceptors detect changes in muscle length, volume (ie, muscle loss or wasting), and by-products of muscle metabolism and stimulate group III-IV afferents of the spinal cord to the medullary respiratory centers to stimulate ventilation.[34,35] Muscle weakness and fatigue are a common manifestation of post-COVID-19 syndrome,[36] even among those who experienced mild COVID-19.[37] It is possible that, in the patients who have recovered from COVID-19, similar to heart failure patients, a skeletal muscle myopathic process characterized by a shift in fiber type,[38] reduced muscle aerobic enzyme activity with early dependance on anaerobic metabolism,[39] or both culminate in overactivation of group III-IV skeletal muscle afferent activity with resulting exaggerated hyperventilation.

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Results from the current study need to be interpreted in the context of limitations. Data for this study were drawn from a small number of patients who had recovered from COVID-19. However, the peripheral limitation to exercise intolerance exhibited by the patients who recovered from COVID-19 were striking compared with those of control participants, and the finding of ventilatory inefficiency (ie, abnormal VE to VCO_2 ratio slope) is in keeping with a recent report.[13] Additionally, by using iCPET, we provided a comprehensive and unparalleled insight into the long-term sequelae of SARS-CoV-2 infection that is otherwise not apparent on conventional investigative testing.

The control participants were derived from iCPET evaluation for unexplained exertional dyspnea, and therefore, the control participants may not be representative of a completely healthy population. However, the control participants were selected based on a preserved peak exercise capacity defined by a normal cardiac limit to exercise (peak VO_2 and peak CO of ≥ 80% predicted). Therefore, they represent a studied population with a normal physiologic response to exercise and reflect so-called symptomatic normal individuals.

Interpretation

Exercise limitation is common manifestation of post-COVID-19 syndrome months after resolution of mild acute COVID-19 illness. A peripheral, rather than a central, cardiac limit to exercise characterized by diffusion defect in oxygen delivery (ie, impaired systemic EO_2) contributes to patients who have recovered from COVID-19 demonstrating a depressed aerobic exercise capacity. Additionally, patients who have recovered from COVID-19 also exhibit an exaggerated hyperventilatory response during exercise. Further studies are warranted to investigative the pathobiologic basis of these mechanisms.

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